Phentermine/Topiramate (QSYMIA)

National Drug Monograph

April 2013

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- The mean body mass index (BMI kg/m^2) of Veterans as increased every year since 2002. The prevalence of obesity (BMI≥30) in 2011 was 39.8%. These findings are reflective of OEF/OIF veterans as well as the veteran population in general.
- Being overweight or obese is associated with a number of chronic conditions including type 2 diabetes, hypertension, sleep apnea, hyperlipidemia and stroke. Weight loss has been shown to improve or reduce the risk for developing weight-related comorbidities.
- Phentermine/topiramate (P/T) extended-release capsules has an FDA label indication as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of:
    - 30 kg/m^2 or greater (obese) or
    - 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, obstructive sleep apnea, and degenerative joint disease/osteoarthritis.
- Phentermine/topiramate requires a dosage titration to a maintenance dose P7.5mg/T46mg each morning which should be maintained for 12 weeks. If after 12 weeks 3% of baseline body weight has not been lost, then the dose can be titrated to the maximum dose of P15 mg/T92 mg each morning. If after 12 weeks 5% of baseline body weight has not been lost, the P/T should be tapered and discontinued.
- Phentermine/topiramate is Schedule IV.
- Phentermine/topiramate is contraindicated in pregnancy and patients with glaucoma, hyperthyroidism, and use of an MAOI in the past 14 days and known hypersensitivity.
- In two pivotal clinical trials submitted to FDA, P15/T92 dose resulted in a mean percentage of body change in body weight of -10.9 and -9.8, respectively, compared to -1.6 and -1.2 with placebo. The proportion of patients losing >5% of body weight with P15/T92 was 67% and 70%, respectively compared to 17% and 21% with placebo. Only one study included a P7.5/T46 resulting in a -7.8% mean change in body weight and 62% of patients losing at least 5% of body weight.
- Significant secondary benefits were seen with P/T compared to placebo in systolic and diastolic blood pressures, weight circumference, glycemic control and lipid profiles. The net change in medications for hypertension, type 2 diabetes, and hyperlipidemia favored P/T.
- The safety of the combination was an extension of its two components with paresthesia, dizziness, dysgeusia, insomnia, constipation and dry mouth the most frequently reported adverse effects. Other adverse effects include metabolic acidosis, hypokalemia, kidney stones, and dose-related disturbances in attention, concentration and memory.
- Phentermine/topiramate is FDA Pregnancy Category X due topiramate's association in oral cleft abnormalities. A REMS program is required to minimize use in pregnancy.

Introduction[1-4]

Obesity has never been more prevalent among veterans. The mean body mass index (BMI, kg/m^2) of veterans receiving care from VHA has increased every year since FY2002 through 2011; 28.7 to 29.4. The same pattern is true for the percent of veterans who are obese (BMI $\geq$30) which was 34.7% in 2002 and was 39.8% in 2011. The 2011 prevalence of obesity was 35%-39% in 7 VISNs and $\geq$40% in the remaining 14 VISNs. Among OEF/OIF veterans only one VISN had a prevalence of obesity between 30%-34%. The prevalence of obesity in OEF/OIF veterans was $\geq$40% 10 VISNs. Over 77% of Veterans receiving care from VHA are either overweight (BMI 25-29.9) or obese.

Veterans who are overweight or obese are at greater risk for developing hypertension, diabetes, dyslipidemia, cardiovascular disease, stroke, obstructive sleep apnea, and some types of cancers. Overweight and obese women are at increased risk for developing infertility and menstrual irregularities. Clinical trials have demonstrated that weight loss improves blood pressure, cholesterol, glycemic control, and obstructive sleep apnea and reduces incident hypertension and type 2 diabetes. There is no direct evidence from prospective clinical trials demonstrating that weight loss reduces cardiovascular morbidity and mortality. It is well established that mortality begins to increases in a linear fashion starting with a BMI of 25.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating phentermine/topiramate (P/T) as part of a treatment strategy for weight loss and weight maintenance for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[5]

Phentermine is a sympathomimetic amine similar in activity to amphetamine including anorectic or anorexigenic properties. Phentermine is believed to reduce appetite and decrease food intake through mediation of catecholamine release in the hypothalamus. Other metabolic effects may be involved.

Topiramate's mechanism of action as a chronic weight management drug is unknown. Appetite suppression and satiety enhancement may be due to one or a combination of several effects including augmentation of gamma-aminobutryate, modulation of voltage-gated ion channels, inhibition of AMPA/kainite excitatory glutamate receptors, or inhibition of carbonic anhydrase.

Table 1 Pharmacokinetic parameters of phentermine/topiramate ER capsules

Parameter	Phentermine 15 mg	Topiramate 92 mg ER
Bioavailability		
Cmax	49.1 ng/mL	1020 ng/mL
Tmax	6 hr	9 hr
$AUC_{0-\infty}$	2000 ngxhr/mL	68000 ngxhr/mL
Distribution		
Protein binding	17.5%	15-41% (↓ as conc.↑)
Volume of distribution	349 L	Vc/F 50.8 L; Vp/F 13.1 L
Metabolism	CYP 3A4 hydroxylation and oxidation	<5% metabolized
Excretion, urine	70%-80% unchanged	~70%
Terminal half-life	20 hr	65hr

FDA Approved Indication(s)[5]

As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, obstructive sleep apnea, and degenerative joint disease/osteoarthritis.

Phentermine/Topiramate is Schedule IV.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Use by persons with a BMI less than 27, i.e., casual weight loss.

Current VA National Formulary Alternatives

None

Dosage and Administration[5]

Dose Titration

- One phentermine 3.75 mg/topiramate 23 mg extended-release capsule in each morning for 14 days; then increase to 7.5 mg/46 mg each morning for an additional 12 weeks.
- If a weight loss of 3% of baseline body weight is not achieved increase the dose to 11.25 mg/69 mg each morning for 14 days; then increased to 15 mg/92 mg (maximum dose) each daily.
- If after 12 weeks on 15 mg/92 mg the patient has not lost at least 5% of baseline body weight, discontinue phentermine/topiramate, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.
- The 3.25 mg/23 mg and 11.25 mg/69 mg formulations are for titration purposes only.
- Discontinuation of phentermine 15 mg/ topiramate 92 mg gradually by taking a dose every other day for at least 1 week prior to stopping the medication altogether, due to the possibility of precipitating a seizure.

Dose in Patients with Renal Impairment

- The dose for patients with an estimated creatinine clearance using the Cockcroft-Gault equation of <50 mL/min (moderate to severe renal impairment) should not exceed 7.5 mg/46 mg once daily.
- Phentermine/topiramate has not been studied in patients with end-stage renal disease on dialysis and should be avoided in this patient population.

Doses in Patients with Hepatic Impairment

- A dose adjustment is not necessary in patients with mild hepatic impairment (Child-Pugh score 5-6).
- The dose for patients with moderate hepatic impairment (Child-Pugh 7-9) should not exceed 7.5 mg/46 mg once daily.
- Phentermine/topiramate has not been studied in patients with severe hepatic impairment (Child-Pugh 10-15) and should be avoided in this patient population.

Risk Evaluation and Mitigation Strategy (REMS)

- Phentermine/topiramate is subject to a REMS program to inform prescribers and female patients of the reproductive risks.

- Phentermine/topiramate is a specialty distribution weight management medication. And is only available by mail order through certified pharmacies in the Qsymia™ Home Delivery Network. The manufacturer has contracted with Express Scripts/Accredo Specialty Pharmacy to service VA and the product cannot be purchased as a wholesale transaction. The following steps are involved :
    - Prescriber completes the prescriber section of the VA-specific Qsymia™ Pharmacy Fax Form and submits to the VA pharmacy along with the prescription with the provider's DEA number
    - The VA pharmacy reviews the prescriber section of the form and completes the second half of the document
    - The prescription is taped to a blank sheet and faxed along with the VA-specific Qsymia™ Pharmacy Fax Form to the Accredo Health Qsymia™ Specialty Pharmacy 877-329-4620
    - Accredo Health Qsymia™ Specialty Pharmacy calls the VA Pharmacy for payment information and then dispenses and ships the prescription directly to the patient. The prescription cannot be sent to the VA facility
    - Accredo Health Qsymia™ Specialty Pharmacy faxes the Qsymia VA Delivery Confirmation Summary to the VA pharmacy within 72 hours of the patient receiving the medication.

Efficacy

Efficacy Measures[6]

FDA uses two measures to establish the efficacy of weight-loss medications. The first, a mean efficacy criterion, is a statistically significant difference in mean weight loss of at least 5% between active drug and placebo groups. The second, a categorical efficacy criterion, includes the loss of at least 5% of baseline body weight in at least 35% of participants in the active drug group; such weight loss in approximately double the proportion of participants in the active drug group as in the placebo group; and a significant difference between groups.

Summary of efficacy findings

Weight Loss

Topiramate monotherapy[7-8]

Weight loss was noted as an adverse effect to topiramate when used to treat epilepsy. Between 6% - 16% of patients exposed to topiramate will report weight loss. Weight loss is most likely in the first 3 months of treatment (82%). A mean of 3.9 kg is lost at 3 months and 5.9 kg at 1 year. The amount of weight lost is greater the greater a patients body weight or BMI. Weigh loss usually begins in the first month of exposure and has been noted to continue as long as 13 months with sustained fat loss. A decrease in body fat mass accounts for 60% –70% of weight lost in epileptics. Fat loss was greatest in persons with a BMI >30 at 1.6% per month for the first 3 months, then 1.4% per month for the next 9 months for a cumulative loss of 18% in 1 year. Data from trials in patients with epilepsy are inconclusive about a dose response relationship. Studies which have identified greater weight loss with increasing dose have reported a ceiling effect at 192 mg/day.

A meta-analysis that included 3320 individuals from 10 studies (19 treatment arms) comparing topiramate (64 mg – 400 mg/day as a weight loss agent) to placebo over periods of 16 to 60 weeks found the mean weight loss experienced by patients taking topiramate was 5.34 kg (9% CI -6.12 to -4.56 kg) greater than with placebo. The probability that a patient taking topiramate would lose ≥5% of their body weight was 6.02 times that of placebo (95% CI 5.48 to 9.36) with a NNT = 3.7. The amount of weight lost was a function of both increase dosage and duration of exposure. Topiramate's effect on HbA_{1c} was included in 4 trials; patients with diabetes had a mean reduction in HbA_{1c} of -0.43% (-0.57 to -0.25%). Safety data were available for 6620 patients. The risk of study withdrawal due to an adverse event was greater for topiramate treated patients (OR 1.95, 1.64-2.29). The dose of topiramate was directly associated with

adverse events leading to withdrawal: up to 96 mg/day OR 1.6 (1.23-2.1), 96-200 mg/day OR 2.18 (1.70-2.80), and >200 mg/day OR 2.19 (1.40-3.38). This same dose-related pattern was observed with the most common adverse events including paresthesia, taste perversion, psychomotor impairment, hypoesthesia, difficulty concentrating, anorexia, memory impairment and nervousness.

Phentermine/Topiramate[9-11]

EQUIP was a double-blind, placebo-controlled, parallel-group, randomized trial lasting 56 weeks and conducted 91 U.S. centers. Eligible participants had a BMI ≥35, triglycerides ≤ 200 mg/dL on 0-1 lipid lowering drugs, BP ≤ 140/90 mmg Hg on 0-2 antihypertensives and a fasting blood glucose (FBS) ≤ 110 mg/dL. All participants were enrolled in standardized lifestyle program and advised to decrease their daily caloric intake by 500 kcal, increase water consumption, and increase their physical activity. Participants were randomized to placebo, P 3.75/T 23, or P 15/T 92 in a 2:1:2 ratio. Weeks 1 – 4 were used to titrate subjects to their assigned dose. Primary outcome measures at Week 56 were percent of weight loss from baseline, and percent of participants who lost ≥5%, ≥10% or ≥15% of baseline body weight. Secondary outcomes were change in waist circumference, systolic and diastolic blood pressures, triglycerides, total cholesterol, LDL, HDL, TC/HDL and FBS at 56 weeks. Three analyses were performed: A – an intention-to- treat (ITT) with last observation carried forward (LOCF) per FDA standards, B – per protocol (prespecified) and C – all randomized patients.

A total of 1267 persons were enrolled and randomized. At baseline the mean age was 42.5 years, mean BMI 42, 83% were women and 16-18% were African American. Primary outcome results are shown in Table 2. Weight loss (in kg and as percent losing ≥5%, 10% and 15%) was significantly greater in patients assigned to both P/T groups than placebo. The measures were significantly greater in the P15/T92 group than the P3.75/T23 group. Changes in secondary outcomes in the P15/T92 group were significantly different from placebo and the P3.75/T23 groups in all measures except FBS (Table 3).

Table 2 Weight loss by treatment group and analysis EQUIP

Outcome/Analysis	Placebo	T3.75/P23	T15/P92
No. randomized	514	241	512
% Completed	52.9	61.0	66.4
% Full course treatment	46.9	57.3	58.8
% Loss of BW			
ITT- LOCF (n)	1.6% (498)	5.1% (234)	10.9% (498)
Completed study	2.1%	6.7%	14.4%
ITT Loss of BW			
≥5%	17.3%	44.9%	66.7%
≥10%	7.4%	18.8%	47.2%
≥15%	3.4%	7.3%	32.3%
Completers Loss of BW			
≥5%	25.5%	59.1%	83.5%
≥10%	13.0%	27.7%	67.7%
≥15%	5.9%	12.4%	48.1%

BW = body weight

Table 3 EQUIP Secondary Measures: Least Square Mean Change (95% CI) from baseline

Outcome/Analysis	Placebo	T3.75/T23	T15/T92
Waist Circumference			
Baseline mean, cm	120.5	121.7	120.1
LSMΔ	-3.1 (-4.0, -2.2)	-5.6 (-6.8, -4.3)	-10.9 (-11.8, -10.0)
SBP			
Baseline mean, mm Hg	121.8	122.5	122.0
LSMΔ	0.9 (-0.2, 2.1)	-1.8 (-3.4, -0.3)	-2.9 (-4.0, -1.8)

DBP Baseline mean, mm Hg LSMΔ	 77.2 0.4 (-0.40, 1.2)	 77.8 -0.1 (-1.2, 1.0)	 77.4 -1.5 (-2.4, -0.6)
Fast glucose Baseline mean, mg/dL LSMΔ	 93.0 1.9 (1.0, 2.9)	 93.8 0.8 (-0.5, 2.1)	 93.0 -0.6 (-1.5, 0.4)
Triglycerides Baseline mean, % LSM%Δ	 118.8 9.1 (4.7, 13.5)	 116.7 5.2 (-2.4, 12.6)	 114.0 -5.2 (-9.6, -0.8)
Total cholesterol Baseline mean,% LSM%Δ	 194.7 -3.5 (-4.7, -2.2)	 196.1 -5.4 (-7.1, -3.7)	 192.5 -6.0 (-7.3, -4.8)
LDL cholesterol Baseline mean, % LSM%Δ	 121.3 -5.5 (-7.4, -3.7)	 122.5 -7.7 (-10.3, -5.2)	 119.8 -8.4 (-10, -6.5)
HDL cholesterol Baseline mean, % LSM%Δ	 49.5 0 (-1.6, 1.6)	 50.2 0.5 (-1.7, 2.7)	 49.8 3.5 (1.9, 5.1)

SBP = systolic blood pressure, DBP = diastolic blood pressure, LSM%Δ = Lease-square mean percent change

CONQUER was a randomized, double-blind, placebo controlled trial conducted in 93 U.S. centers. Like EQUIP, it consisted of a 4-week post randomization, blinded dose titration phase followed by a 52-week study period. Enrollment criteria consisted of age 18-70, a BMI of 27 – 45 kg/m^2 and at least two of the following:

- SBP 140-160 (130-160 if diabetic) mm Hg
- DBP 90-100 (85-100 if diabetic) mm Hg
- Prescribed 2 or more antihypertensive medications
- Triglycerides 230 – 400 mg/dL or prescribed 2 or more lipid lowering drugs
- FBS > 100 mg/dL
- Glucose tolerance at 2 h >140 mg/dL
- Type 2 diabetes mellitus with either lifestyle management or metformin monotherapy
- Waist circumference ≥40 inches men; ≥35 inches women

Exclusion criteria consisted of measures outside the above parameters, a history of nephrolithiasis, recurrent major depression disorder, or history of suicidal behavior, or ideation with intent and a PHQ-9 score ≥10. Eligible subjects were randomized (2:1:2) to placebo, P7.5/T46, or P15/T92. All subjects received standardized counseling for diet and lifestyle modifications including instructions to reduce their daily caloric intake by 500 kcal. Primary outcome measures were mean percent change in body weight and percent of subjects with ≥5% loss of body weight. Secondary measures included absolute weight loss and percent of subjects with ≥10% loss of body weight. Three analyses were performed: Primary – an ITT with LOCF; Sensitivity – includes all randomized subjects with missing data estimate; and Completers – all subjects receiving study drug and with an assessment within 7 days of the study's final endpoint.

A total of 2487 subjects were randomized. Study participants had a mean age of 51 years, 70% were women, 86% white and 11% black, mean weight 103 kg and a mean BMI of 36.6. The prevalence of comorbidities was as follows:

- 52% hypertension
- 36% elevated triglycerides
- 68% impaired glucose tolerance or diabetes

- 51% 3 or more protocol comorbidities
- 17% history of depression
- 16% taking an antidepressant

Changes in body weight and the proportion of subjects attaining a ≥5% or ≥10% loss of body weight were significant for both doses of P/T (Table 4). The percent of weight loss from baseline was significant for both doses of P/T for men (7.5/46, 7.5%; 15/92, 9.1%; placebo 2.2%) and women (8.8%, 11.0%, and 1.6%, respectively).

Tables 4 CONQUER Results: Primary and Secondary Outcomes

Measure	Placebo	P7.5/T46	P15/T92
No. randomized	994	498	995
ITT analysis, n	979	488	981
Δ BW, kg	-1.4	-8.1	-10.2
LS mean Δ BW	-1.2%	-7.8%	-8.6%
≥5% loss in BW	21%	62%	70%
≥10% loss in BW	7%	37%	48%
Completer analysis, n	557	338	981
Δ BW, kg	-1.8	-9.9	-12.9
LS mean Δ BW	-1.6%	-9.6%	-10.8%
Diabetics, n	144	63	150
LS mean Δ BW	-1.9%	-6.8%	-8.8%
Δ from placebo	--	4.9%	6.9%

BW = body weight

The decrease in FBS in pre-diabetics was greatest in the P/T treatment arms than the placebo arm and the mean change in fasting insulin concentration in the placebo group was +6pmol/L and declined by ~30 pmol/L in those assigned to P/T. The risk of developing Type 2 diabetes was lower compared to the placebo with P7.5/T46 (RR 0.78, 95% CI 0.4-1.5) and P15/T92 (RR 0.47, 0.25-0.88). The use of antidiabetic medication increased more in the placebo arm (23/157, 15%) than in P7.5/T46 (3/67, 4%) and P15/T92 (7/164, 4%) treatment groups, while the change in glycosylated hemoglobin values was greater with P/T, -0.4% (both groups), than with placebo -0.1%.

Significant improvements in secondary measures including waist circumference were found with both doses of P/T compared to placebo (Table 5). On average SBP and DBP decreased in all three treatment arms, however the changes were significantly greater in both active treatment arms compared to placebo (Table 5). Subjects in the P15/T92 had significant improvement in total cholesterol, HDL-C and triglycerides, while the lower dose P/T group had significant improvements in HDL-C and triglycerides. These changes were also significant in subjects deemed to be at high risk because of comorbidities.

Table 5 CONQUER Secondary Measures: Least Square Mean Change from baseline

Outcome/Analysis	Placebo	P7.5/T46	P15/T92
Waist Circumference			
Baseline mean, cm	113.45	112.7	113.2
LSMΔ	-2.4	-7.6	-9.2
SBP			
Baseline mean, mm Hg	128.9	128.5	127.9
LSMΔ	-2.4	-4.7	-5.6
DBP			
Baseline mean, mm Hg	81.1	80.6	80.2
LSMΔ	0.4 (-0.40, 1.2)	-0.1 (-1.2, 1.0)	-1.5 (-2.4, -0.6)

Fast glucose Baseline mean, mg/dL LSMΔ	 106.6 -2.3	 106.2 -0.1	 105.7 -1.3
Triglycerides Baseline mean, mg/dL LSM%Δ	 159.4 4.7	 159.4 -8.6	 159.4 -10.6
Total cholesterol Baseline mean, mg/dL LSM%Δ	 204.6 -3.3	 200.8 -4.9	 204.6 -6.3
LDL cholesterol Baseline mean, mg/dL LSM%Δ	 123.6 -4.1	 119.7 -3.7	 123.6 -6.9
HDL cholesterol Baseline mean, mg/dL LSM%Δ	 50.2 +1.2	 50.2 +5.2	 50.2 +6.8

Table 6 CONQUER: Mean Changes in Blood Pressure and Lipids in Subjects with Pre-existing comorbid conditions (High Risk)

Measure	**Placebo**	**P7.5/T46**	**P15/T92**
SBP, mm Hg	-4.9	-6.9	-9.1
DBP, mm Hg	-3.9	-5.2	-5.8
Total Cholesterol, %	-4.9	-5.7	-7.8
LDL-C, %	-3.6	+0.7	-4.3
HDL-C, %	+2.8	+9.5	+10.7
Triglycerides, %	-8.8	-24.1	-25.6

SEQUEL was a randomized, placebo-controlled, one-year extension of CONQUER. Subjects were eligible for SEQUEL if they completed treatment and the protocol requirements of CONQUER and their study site was selected to participate. Subjects were excluded if their BMI ≤22 at the end of CONQUER or failed to comply or developed a condition during CONQUER that would prevent compliance with the SEQUEL protocol. Subjects remained assigned to their original CONQUER treatment arm along with lifestyle interventions. Thirty-six of the 93 CONQUER sites with high initial enrollment and retention rates were asked to participate in SEQUEL. Primary outcome measures were the same as SEQUEL. Secondary endpoints included weight loss, percent of subjects with >5%, >10% or >20% weight loss, and waist circumference. Additional measures included changes in blood pressure, diabetes and glycemic control, lipids and drug use to control hypertension, diabetes, and hyperlipidemia. Analysis was based on changes from CONQUER baseline to week 108 (end of SEQUEL).

A total of 676 (78.1%) of CONQUER subjects enrolled in SEQUEL; 84% completed SEQUEL. Between 65% and 70% of subjects met the AHA and NHLBI criteria for metabolic syndrome. Primary outcome findings are shown in Table 7 and were significantly improved with both P/T groups compared to placebo.

Table 7 SEQUEL Results: Primary and Secondary Outcome Measures at Week 108

Measure	**Placebo**	**P7.5/T46**	**P15/T92**
ΔBW from baseline	-1.8%	-9.3%	-10.5%
LS mean weight loss, kg	-2.1	-9.6	-10.9
% BW loss ≥5% ≥10% ≥15%	 30% 11.5% 6.6%	 75.2% 50.3% 24.2%	 79.3% 53.9% 31.9%

≥20%	2.2%	9.2%	15.3%
ΔWC, cm	-3.6	-9.8	-10.6
BW loss T2D	2.0%	9.0%	9.0%

Changes in Weight-related Co-morbidities and Medication

Both SBP and DBP improved significantly in all three treatment arms by the end of SEQUEL except the change in SBP in the placebo arm. These changes were not significant between the three treatment arms. The percent of subjects with a net change in antihypertensive medications decreased in both P/T groups and increased in the placebo group. Similar net changes in lipid lowering and diabetes medications were reported (Table 8).

Table 8 SEQUEL: Changes in Secondary Outcome Measures at Week 108

Measure	Placebo	P7.5/T46	P15/P92
LS mean Δ SBP, mm Hg	-3.2	-4.7	-4.3
LS mean Δ DBP, mm Hg	-3.9	-3.7	-3.5
% subj. with net Δ in BP meds	+3.5	-3.9	-3.5
LS mean Δ, %			
Triglycerides	+0.4	-12.5	-13.7
HDL-C	+4.7	+7.3	+11.9
LDL-C	-10.7	-4.6	-5.6
Non HDL-C	-9.7	-9.0	-9.3
% subj. with net Δ in lipid meds	+17.2	+5.2	+4.7
Subj. with T2 DM			
LS mean Δ HbA1c, %	-0.04	-0.4	-0.6
% subj. with net Δ DM meds	+7.1	+1.9	0.0
LS mean Δ FBS, mg/dL	+3.7	+0.1	-1.2
LS mean Δ Fasting Insulin, uIU/mL	-2.6	-5.3	-5.2
LS mean Δ HbA1c, %	+0.2	+0.01	0.0

DM = diabetes mellitus

Adverse Events (Safety Data)[5, 9-11]

Deaths and Other Serious Adverse Events

Serious adverse events were reported by 2.5% of subjects in each treatment group in EQUIP. One serious drug-related adverse drug event was reported in each of the P/T groups and 2 in the placebo arm. Serious adverse events in CONQUER were reported in 4%, 3%, and 5% of subjects assigned to placebo, P7.5/T46 and P15/T92, respectively.

Common Adverse Events

Table 9 Adverse Events (%) Occurring ≥5% and ≥1.5 Times Placebo

Adverse Effect	Placebo (N=1561)	P3.75/T23 (N=240)	P7.5/T46 (N=498)	P15/T92 (N=1580)
Paresthesia	1.9	4.2	13.7	19.9
Dizziness	3.4	2.9	7.2	8.6
Dysgeusia	1.1	1.3	7.4	9.4
Insomnia	4.7	5.0	5.8	9.4
Constipation	6.1	7.9	15.1	16.1
Dry mouth	2.8	6.7	13.5	19.1

Other Adverse Events

Change in heart rate

In the EQUIP trial, a nonstatistical change in mean heart rate from baseline to week 56 of -0.2, -0.3, and +1.2 bpm were reported for participants in the placebo, P3.75/T23, and P15/T92 treat arms, respectively. Similar nonstatistical changes in mean heart rate occurred in CONQUER, -0.1, +0.1, and + 1.4 bpm in the placebo, P7.5/T46 and P15/T92 groups, respectively. A 10 bpm increase or greater was noted on 2 consecutive visits was more common in the P/T groups than placebo. At the end of SEQUEL (week 108), an increase of 0.4, 1.3, 1.7 bpm was reported in patients assigned to placebo, P7.5/T46 and P15/T92, respectively.

CNS effects

A dose-related attention difficulty was reported in 0.6% of subjects assigned to placebo and 0.4%, 2%, and 3.5% assigned to P3.75/T23, P7.5/T46 and P15/T92, respectively. Complaints of loss of attention and concentration, memory, and word finding difficulties generally were noted in the first 4 weeks of treatment, lasted a median of 28 days and reversed upon discontinuation.

Participants in the clinical trials were monitored for depression and mood changes using the PHQ-9. A nonsignificant improvement in depression symptoms was noted in all groups at the end of EQUIP. At the end of CONQUER there was no significant change in PHQ-9 scores or in new antidepressant starts. In SEQUEL, depression was reported as a treatment emergent adverse effect in 7.9% assigned to placebo, 3.9% P7.5/T46, and 8.1% P15/T92. In none of the trials was there an increase in suicide risk, attempts or reports.

Metabolic changes

Bicarbonate

A small, dose-related change in serum bicarbonate concentration was noted in EQUIP and CONQUER, but not in the second year of SEQUEL (Table 10).

Table 10 Changes in Serum Bicarbonate Concentration by Study

Study	Placebo	P3.75/T23	P7.5/T46	P15/T92
EQUIP • Mean Δ [HCO_3], mEq/L • [HCO3] <17 mEq/L x 2	 -0.3 0	 -1.6 3 (1.3%)	 -	 -1.7 4 (0.8%)
CONQUER • Mean Δ [HCO3], mEq/L • [HCO3] <17 mEq/L x 2	 +0.5 1 (0.1%)	 -	 -0.3 1 (0.2%)	 -1.0 7 (0.7%)
SEQUEL (Wk 0-108) • Mean Δ [HCO3], mEq/L • >5 mEq/L ↓ x 2 ○ Weeks 56-108	 +2.2 4 (1.8%) 0	 -	 +0.7 20 (13.1%) 4 (4.6%)	 +0.2 48 (16.3%) 12 (4.1%)

Hypokalemia
A small, dose-dependent decrease in serum potassium was noted in CONQUER (1-3%) with a persistent serum potassium <3.5 mEq/L noted in 1% taking placebo, 4% taking P7.5/T46 and 5% taking P15/T92. Potassium supplementation was needed in 4%, 4% and 5% of participant in each respective treatment arm.

Tolerability
Data from the EQUIP, CONQUER and SEQUEL trials suggest that drug-related adverse events resulting in study discontinuation were dose related (Table 11).
Table 11 Frequency of Drug-related Study Discontinuation

Study	Placebo	P3.75/T23	P7.5/T46	P15/T92
EQUIP	8.4%	11.3%	-	16%
CONQUER	9%	-	12%	19%
SEQUEL (Wk 0-108)	3.1%	-	4.5%	4.4%

Contraindications[5]

- *Pregnancy* – FDA Pregnancy Category X because of the increased risk of oral clefts associated with topiramate and weight loss is not recommended for pregnant women. A total of 17 pregnancies were reported in EQUIP and SEQUEL. The one pregnancy reported in a women assigned to placebo resulted in a miscarriage at 6 weeks. Of the 16 pregnancies in women taking phentermine/topiramate 10 resulted in healthy births, 3 spontaneous abortions and 3 elective abortions. No congenital malformations were reported.
- *Glaucoma* – acute myopia with secondary angle closure glaucoma has been reported in patients receiving topiramate.
- *Hyperthyroidism*
- During or within 14 days following the administration *of monoamine oxidase inhibitors*
- Known *hypersensitivity* or idiosyncrasy to the sympathomimetic amines.

Warnings and Precautions[5]

- *Increased heart rate* – the phentermine/topiramate combination can cause an increase in resting heart rate. The clinical significance of the increase is unclear, especially in patients with cardiovascular or cerebrovascular disease. The combination has not been studied in patients with recent or unstable cardiac or cerebrovascular disease and use is not recommended in these patients.
- *Suicidal behavior and ideation* – because the combination includes topiramate, an antiepileptic drug, this warning has been extended to the combination product. See Adverse Events for additional information.
- *Acute myopia and secondary angle closure glaucoma*
- *Mood and sleep disorders* – see Adverse Events for additional information
- *Cognitive impairment* – patients should exercise caution when operating hazardous machinery. See Adverse Events for additional information.
- *Metabolic acidosis* – hyperchloremic, non-anion gap, metabolic acidosis has been reported. Reduce the dose or discontinue if metabolic acidosis is persistent. Use with caution in patients taking a carbonic anhydrase inhibitor.
- *Elevation in creatinine* – if persistent, either discontinue or reduce the dose.
- *Potential hypoglycemia in type 2 diabetics on anti-diabetic therapy* – weight loss may increase the risk of hypoglycemia necessitating a decrease in the dose of anti-diabetic medications.
- *Potential hypotension in patients treated with antihypertensive medication* – weight loss may result in a reduction in blood pressure and possibly hypotension necessitating a decrease in the dose of antihypertensive medications.
- *CNS depression with concomitant CNS depressants including alcohol*

- *Potential seizures with abrupt withdrawal of topiramate* – regardless of seizure history. It is recommended that patients taking the 15 mg/92 mg dose have their dose tapered prior to discontinuation.
- *Patients with renal impairment* – adjust dose based on estimated creatinine clearance. See Dosage and Administration.
- *Patients with hepatic impairment* – adjust dose for patients with moderate hepatic impairment. See Dosage and Administration.
- *Kidney stones* – topiramate has been associated with kidney stone formation. Concurrent use of other drugs that inhibit carbonic anhydrase or a ketogenic diet may increase the risk.
- *Oligohidrosis and hyperthermia* – has been reported with the use of topiramate. Caution patients to monitor for this adverse effect.
- *Hypokalemia* – inhibition of carbonic anhydrase or use of a non-potassium sparing diuretics may increase risk.

Monitoring[5]

Obtain blood bicarbonate, creatinine, potassium and glucose at baseline and periodically during treatment.

Special Populations[5]

Pregnancy

Phentermine/topiramate is FDA Pregnancy Category X and is contraindicated in pregnancy. Women of reproductive potential should avoid getting pregnant while taking the combination and discontinue taking phentermine/topiramate should they become pregnant. It is recommended that a pregnancy test be performed before starting treatment and monthly thereafter while taking phentermine/topiramate. Women of reproductive potential are to be advised to use effective methods of contraception via the REMS program.

Nursing Mothers

Topiramate and phentermine are excreted in human milk. To avoid exposing a nursing infant to either drug, women choosing to nurse should discontinue the drug. Women who choose to continue the drug should not nurse.

Geriatric Use

Only 7% (254) of subjects in clinical trials were 65 years of age or older and was insufficient to determine if their response differed from younger subjects. No overall safety or efficacy differences were observed.

Renal or Hepatic Impairment – See Dosage and Administration

Postmarketing Safety Experience

Ten postmarketing studies were mandated as part of phentermine/topiramate's approval. These studies are not completed and summarized below.

- Two pharmacokinetic/pharmacodynamics studies in 7-11 year olds and 12-17 year olds
- Two 52-week safety and efficacy trials in 7-11 year olds and 12-17 year olds
- A juvenile animal study on memory, learning and behavior
- An in vitro study to determine the inhibition potential of both phentermine and topiramate extended-release individually and in combination on the following human transporters: organic cation transporter2 (OCT2) and OCT3; organic anion transporter3 (OAT3) and OAT4; multidrug and toxin extrusion protein1 (MATE1) and MATE2-K.
- A prospective cohort study to a) determine the frequency of pregnancy in women of child-bearing age prescribed phentermine/topiramate and b) compare the risk of oral clefts, major congenital malformations, and low birth weight in offspring of women exposed to phentermine/topiramate

during pregnancy with offspring of similar women not exposed to phentermine/topiramate during pregnancy.

- A drug-use study conducted annually for 7 years with nationally representative and projected data to provide a denominator in order to assess adverse event reporting rates of the known serious risk of congenital malformation (specifically orofacial clefts) in infants exposed to phentermine/topiramate during the first trimester of pregnancy, and to assess possible risk factors contributing to the risk.
- A randomized, placebo- and active-controlled trial to evaluate changes in renal function in obese adults, who will be randomized to phentermine/topiramate (3 dosage strengths) or placebo.
- A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with phentermine/topiramate on the incidence of major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors. A subset of individuals should have measurements of bone health assessed by serial radiographic and laboratory measurements.

Sentinel Events

None

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:
LA/SA for generic name *PHENTERMINE*: *Adipex-P, Suprenza, phentolamine, phenytoin*
LA/SA for generic name *TOPIRAMATE: Topamax, Toprol-XL*
LA/SA for trade name *QSYMIA*: *None identified*

Drug Interactions[5]

Drug-Drug Interactions

Monoamine oxidase inhibitors – phentermine is contraindicated during or within 14-days following administration of an MAOI.
Oral contraceptives – a 16% reduction in AUC of ethinyl estradiol and a 22% increased AUC of norethindrone were reported. A reduction in contraceptive efficacy is not anticipated but irregular bleeding (spotting) may be more frequent.
Antiepileptic drugs

- Phenytoin and carbamazepine decrease topiramate concentrations by 48% and 40%, respectively
- Valproic acid in combination with topiramate has been associated with hyperammonemia with or without encephalopathy and hypothermia

Carbonic anhydrase inhibitors – increased severity of metabolic acidosis and increased risk of kidney stone formation
CNS depressants including alcohol – concomitant use may increase sedation and other adverse effects
Non-potassium sparing diuretics – may potentiate potassium loss

Acquisition Costs

Refer to VA pricing sources for updated information.

Conclusions

Given the prevalence of overweight and obesity as well as weight-associated conditions among Veterans, the availability of a medication that decreases appetite is a potentially valuable component of a comprehensive approach to weight loss and maintenance. In clinical trials, the combination of phentermine/topiramate demonstrated its efficacy as part of a weight loss and management strategy.

Compared to placebo, the absolute amount of weight lost, the proportion of patients who lost ≥5% and ≥10% of their baseline body weight, and reductions in waist circumference were significantly greater with the combination. Additional benefits related to weight-loss were reported in patients treated with the combination including reductions in blood pressure, improved glycemic control and lipid profile. The net change in medications used to treat these conditions was also significant with the combination.

The safety of the combination was an extension of its two components. The product is a FDA Pregnancy Category X and a REMS program is required to minimize use in pregnancy. The mean change in heart rate was small, but some patients experienced a >10 bpm increase; the implications of this increase are unknown. Consistent with topiramate's adverse effect profile, dose-related complaints of attention, concentration and memory were reported.

The clinical trials with phentermine/topiramate were not conducted in patients reflective of Veterans. Trial participants were primarily women and less 65 years of age. Thus, it cannot be stated with certainty that the weight loss, other benefits, and the safety profile reported in clinical trials will be realized in the patients cared for by VHA. As outlined in the VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity, and VA MOVE!®, weight loss medications are to be introduced after, and with the continuation of, behavioral interventions to improve diet, reduce daily caloric intake, and increase physical activity.

References

1. VHA Corporate Data Warehouse (CDW-2013). Courtesy of Ken Jones, PhD.
2. Department of Veterans Affairs and Department of Defense Clinical Practice Guidelines for Screening and Management of Overweight and Obesity, 2006. Available at: http://www.healthquality.va.gov/. Accessed November 20, 2012.
3. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
4. Gonzalez AB, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2211-9.
5. Qsymia (phentermine and topiramate extended-release capsules) package insert, July 2012.
6. Guidance for industry: developing products for weight management (draft). Silver Spring, MD: Food and Drug Administration 2007 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071612.pdf. Accessed November 19, 2012.
7. Verrotti A, Scaparrotta A, Agostinelli S, et al. Topiramate-induced weight loss: A review. Epilepsy Research 2011;95:189-199.
8. Kramer CK, Leitao CB, Pinto LC, et al. Efficacy and safety of topiramate on weight loss: a meta-analysis of randomized controlled trials. Obesity Reviews 2011;12:e338-e347.
9. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized control trial (EQUIP). Obesity 2011;20:330-42.
10. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomized, placebo-controlled, phase 3 trial. Lancet 2011;377:1341-52.
11. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr 2012;95:297-308.

Prepared April 2013 Contact person: Todd Semla, MS, Pharm.D., BCPS, FCCP, AGSF